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Validation of a computational platform for the analysis of the physiologic mechanisms of a human experimental model of hemorrhage^{☆,☆☆}

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Abstract

Computational models of integrative physiology may serve as a framework for understanding the complex adaptive responses essential for homeostasis in critical illness and resuscitation and may provide insights for design of diagnostics and therapeutics. In this study a computer model of human physiology was compared to results obtained from experiments using Lower Body Negative Pressure (LBNP) analog model of human hemorrhage. LBNP has been demonstrated to produce physiologic changes in humans consistent with hemorrhage. The computer model contains over 4000 parameters that describe the detailed integration of physiology based upon basic physical principles and established biologic interactions. The LBNP protocol consisted of a 5 min rest period (0 mmHg) followed by 5 min of chamber decompression of the lower body to -15, -30, -45, and -60 mmHg and additional increments of -10 mmHg every 5 min until the onset of hemodynamic decompensation ($n = 20$). Physiologic parameters recorded include mean arterial pressure (MAP), cardiac output (CO), and venous oxygen saturation (SVO₂; from peripheral venous blood), during the last 30 s at each LBNP level. The computer model analytic procedure recreates the investigational protocol for a virtual individual in an *In Silico* environment. After baseline normalization, the model predicted measurements for MAP, CO, and SVO₂ were compared to those observed through the entire range of LBNP. Differences were evaluated using standard statistical performance error measurements (median performance error (PE) <5%). The simulation results closely tracked the average changes observed during LBNP. The predicted MAP fell outside the standard error measurement for the experimental data at only LBNP -30 mmHg while CO was more variable. The predicted SVO₂ fell outside the standard error measurement for the experimental data only during the post-LBNP recovery point. However,

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Conflicts of interest

The authors have no known conflicts of interest relative to this study. Support from NSF EPSCoR and NIH Grant HL-51971.

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the statistical median PE measurement was found to be within the 5% objective error measure (1.3% for MAP, -3.5% for CO, and 3.95% for SVO₂). The computer model was found to accurately predict the experimental results observed using LBNP. The model should be explored as a platform for studying concepts and physiologic mechanisms of hemorrhage including its diagnosis and treatment.

Keywords

Systems analysis; Validation; Hemorrhagic shock

1. Introduction

Acute hemorrhage results in a cascade of complex physiologic responses involving a daunting number of integrated biologic processes. Traditionally, physiologic studies of hemorrhage have relied almost exclusively on animal models. While this approach has proven to be valuable, it is still impossible to gather complete information concerning the integrative physiologic and cellular responses across all systems. Likewise, the study of hemorrhage in the clinical setting is difficult due to the uncontrolled nature of the clinical environment, the inability to rapidly monitor physiologic responses, and the natural variations in injury patterns.

Conventional statistical analyses are commonly used to determine the significance of changes in biomedical experimental data during a perturbation. However, these methods provide very little insight into the biologic mechanisms responsible for the observed changes. Computational modeling has been advocated as an alternative methodology for providing a better comprehension of the mechanics of these complex physiologic responses.¹⁻⁵ Detailed computer models of human physiology can serve as a theoretic framework for the advanced analysis of biomedical concepts and experimental data from a mechanistic and systems perspective.¹⁻⁵ Such a computational platform may also provide for a deeper understanding of the complex adaptive responses essential for homeostasis in critical illness and resuscitation and provide insights for the design of diagnostics and therapeutic strategies. Using these advanced analytic tools, the relative importance of even the most remote clinical findings might have new significance within the context of broad physiologic meaning. However, such models should be objectively validated by comparison to experimental outcomes whenever possible in order to have credibility and provide more consequential conclusions.^{2,4} In this study the predictions of a well-established integrative computer model of human physiology were compared to results obtained from human experiments using Lower Body Negative Pressure (LBNP), an analog demonstrated to produce physiologic changes in humans consistent with hemorrhage.

2. Methods

2.1. The computational platform

The computational platform describing the integrative physiologic functioning of a virtual subject is a special adaptation of an established computer model of human physiology (Guyton/Coleman/Summers model) developed over the past 30 years.⁶⁻¹¹ The model contains over 5000 parameters that describe the detailed integration of systemic, tissue and cellular physiology based upon basic physical principles and established biologic interactions. The structure of the model incorporates the physiologic responses to changes in pressures, flows and hydraulics within the circulatory system as well as the utilization and mass balance fluctuations of metabolic substrates. The details of this model structure are beyond the scope of the current paper and have been described in previous publications.¹²⁻

¹⁵ The schematic in Fig. 1 depicts the basic physiologic interrelationships involved in the circulatory control mechanisms within the core structure of the mathematical model. These mechanisms for circulatory control also drive the delivery of metabolic substrates and are central to the determination of the parameters validated in the computer simulation study and systems analysis.

An early, less-detailed version of this computational platform has been previously demonstrated to accurately predict hemodynamic changes seen during hypotensive states.¹⁶ Applying a mathematically simulated negative pressure to the lower body of the virtual subject, the current model also produces a fluid (blood and plasma) displacement that is similar in quantity to that described in the literature from human experiments using the LBNP methodology over a wide range of pressures (see Table 1).¹⁷ These fluid displacements correspond to the amount of blood volume expected to be lost in a standard classification of hemorrhage. These evidences suggest that the model can be used as a platform for the theoretical analysis of hemorrhagic shock states.

The software interface supporting the computational platform is designed to provide for simple interaction of the user through a desktop platform with current personal computing technology.¹² The model and software support system allows for complex systems studies and theoretical hypothesis testing on specific research questions. The model structure is specified in compiled C++ code in a component-based format (kidney, liver, circulation, etc) with a top down profile (molecular to cellular to organ to system to whole body).

2.2. The experimental protocol

2.2.1. Study design, setting, and population—This human data used in our computational analysis was provided from a previously performed study on 20 volunteers undergoing LBNP performed at the U.S. Army Institute of Surgical Research (USAISR) in San Antonio, TX in conjunction with investigators from the Virginia Commonwealth University in Richmond, VA. The 20 volunteers were healthy, normotensive, nonsmoking subjects (9 males, 11 females) with the following age, height and weight ranges (age, 23.1 yrs; height, 171.2 cm; weight, 69.3 kg). This human study (described below) was approved by the Institutional Review Boards of both the USAISR and Virginia Commonwealth University. The physiologic data generated from this previous study was subsequently compared with similar physiologic data created by the computational model described below.

2.2.2. LBNP model description—Consenting subjects had not undergone any special conditioning prior to study and were asked to refrain from alcohol, exercise, stimulants such as caffeine and other nonprescription drugs 24 h prior to testing.

Continuous heart rate (HR) was measured from a standard electrocardiogram (ECG).

Beat-by-beat systolic (SBP) and diastolic (DBP) blood pressures were measured noninvasively using an infrared finger photo-plethysmograph (Finometer[®] Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The Finometer[®] blood pressure cuff was placed on the middle finger of the left hand which, in turn, was laid at heart level. Excellent estimates of directly measured intra-arterial pressures during various physiological maneuvers have been demonstrated with this device.^{18–20} MAP was calculated by dividing the sum of SBP and twice DBP by three. Stroke volume (SV) was measured noninvasively using thoracic electrical bioimpedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC, USA). This technique is based on the resistance changes in the thorax to a low-intensity (4 mA), high-frequency (70 kHz) alternating current applied by band electrodes placed at the root of

the neck at the xiphoid process at the midaxillary line. Ventricular SV was determined via the Kubicek equation: $SV \text{ (in ml)} = \rho \times (L/Z_0)^2 \times LVET \times (dZ/dt)$, where ρ (in ohm/cm) is the blood resistivity, a constant of 135 ohms/cm in vivo; L (in cm) is the mean distance between the inner band electrodes (front and back); Z_0 (in ohms) is the thoracic background impedance; LVET (in seconds) is the left ventricular ejection time; and (dZ/dt) is the maximum height of the dZ/dt peak. Correlation coefficients of 0.70–0.93 have been reported in SV measurements simultaneously made with thoracic electrical bioimpedance and thermodilution techniques.^{22,23} CO was calculated as the product of HR and SV.²¹ These hemodynamic data were sampled at 500 Hz and recorded by data acquisition software (WINDAQ, Dataq Instruments, Akron, OH). A 19-gauge catheter was inserted into an antecubital vein of the right arm for the collection of blood samples pre-LBNP, and during the last 30 s of each LBNP level. The catheter was flushed with saline after each blood draw, and the first 1 ml of blood drawn was discarded. Each blood sample was ~3-ml, drawn into a syringe without stasis, and immediately transferred from the syringe to a chilled tube containing heparin. Whole blood was taken directly from the tube for measurement of peripheral SVO₂ with a blood gas analyzer (AVL Omni Blood Gas Analyzer, AVL Scientific Corporation, Roswell, GA).

Subjects were placed supine with the lower extremities (from below the iliac crest) placed within the LBNP chamber. An airtight seal between the subject and the chamber was created with a neoprene skirt. The LBNP protocol consisted of a 5-min rest period (0 mmHg) followed by 5 min of chamber decompression to -15, -30, -45, and -60 mmHg and additional increments of -10 mmHg every 5 min until the onset of hemodynamic decompensation or the completion of 5 min at -100 mmHg. Hemodynamic decompensation was identified in real time by the attending investigator by at least one of the following criteria:

- a. a precipitous decrease in SBP (>15 mmHg),
- b. a sudden decrease in pulse rate (>15 beats/min); progressive diminution of SBP <70 mmHg,
- c. voluntary subject termination concurrent with the onset of presyncopal symptoms such as loss of color vision, tunnel vision, sweating, nausea, or dizziness.

Physiologic parameters recorded and used for the validations include MAP, CO, and SVO₂, during the last 30 s at each LBNP level.

2.3. In Silico investigational protocol

The investigational procedure using the computational platform and computer model involves recreating the experiment for a virtual subject in an *In Silico* environment.^{24,25} This process requires a re-enactment of the LBNP investigational protocol in a simulation of the original experiment which included the simulated application of LBNP to the lower body of the virtual subject. The virtual subject used in the procedure is considered to be a normal 70 kg male with no previous pathology. In this simulation experiment, the model predicted sequential changes in the prespecified variables of interest were recorded for the same time points chosen for the experimental protocol. These variables were used in the validation process. Though the predicted values for these determined target variables represent the output for a single individual, they are based upon integrative systems interactions of many physiologic parameters and processes which are representative of the collective means and standard errors for the normal population.

2.4. Validation process

There is currently no established process or widely recognized methodology for the validation of large and complex computer models of biologic systems.²⁴ Model validation has been generally defined as the confirmation that a computer model possesses a satisfactory range of accuracy within its domain of applicability and is consistent with the intended use.^{24,25} This emphasis on accuracy in the context of clinical state is our approach to validation of the computational platform used in this study. Most important in this process is the comparison of physiologic endpoints that typify and define the hemorrhagic state to those predicted by the model. The physiologic variables of MAP, CO and SVO₂ were chosen as the validation targets because of their general clinical relevance in this pathologic state and global significance from a physiologic perspective.

While absolute agreement between the model output and experimental findings is not expected, there should be definite measurable criteria by which to judge the validity of the model.^{1,2} Three specific criteria previously described in the literature were used in the validation process of the computational platform and are outlined below.

- Qualitatively—It is important that the model results are directionally appropriate.
- Quantitatively by steady state—Models must demonstrate steady state values that approach those seen experimentally. Standard statistical measures (averages; standard error measurement SEM) were used in the comparison of steady values of physiologic parameters.
- Quantitatively in dynamics—Models must demonstrate responses that are reasonably accurate during dynamic transitions. The overall dynamic performance of the model was quantified by determination of the median performance error (MDPE = median {PE} over all data points as % of measured where PE = difference between measured and predicted values). MDPE has been considered as the measure of the *bias* and *inaccuracy* between the model's predictions and the corresponding experimental observations. This measure has been employed in the validation of algorithms used in drug delivery systems in which precision is of great clinical importance.^{26–29} A commonly considered error margin of 5% was chosen a priori for this study.

In the analysis there was a baseline normalization of CO to body surface area because of the known relationship of this variable to individual subject size. The model predicted measurements for MAP, CO, and SVO₂ were compared to those observed through the entire range of LBNP used in the experimental protocol.

3. Results

In comparison to the results of 20 volunteer subjects, the target outputs of the *In Silico* investigational simulation protocol were found to closely track the average directional changes seen during the experimental LBNP protocol. The graphical results of the comparison of the predicted and experimental results for MAP and SVO₂ are shown in Figs. 2–4. In the analysis of the variables in steady state, the predicted MAP fell outside the SEM for the experimental data at only LBNP –30 mmHg while the predicted SVO₂ fell outside the standard error measurement for the experimental data only during the post-LBNP recovery point. The results of the comparison for CO were more variable over the range of the LBNP values with predicted values outside of the range of SEM at 4 different points including the recovery period. In the analysis of dynamic performance, the statistical MDPE measurement was found to be within the 5% objective error measure chosen a priori for all three target variables (1.3% for MAP, –.5% for CO, and 3.95% for SVO₂).

4. Discussion and conclusions

To derive the full range of physiologic and pathologic meaning from our investigations, it is important to understand the underlying mechanisms responsible and their relative contribution to the control of the entire system. Researchers at the USAISR and others have pioneered the use of LBNP as a model to study the effects of hypovolemia in conscious humans.^{17,30,31} Previous studies have shown that changes in hemodynamics and autonomic responses produced by sequential LBNP are comparable to hemorrhage produced in large animals or mild to moderate blood removal in humans.^{17,30–33} While the model produces changes in CO and MAP that appear to be similar to actual clinical hemorrhage, there is still much to be explored regarding the physiologic mechanisms of microvascular perfusion and tissue oxygenation. In this study, a large integrated computer model of human physiology was found to accurately predict the changes in MAP, CO, and ScVO₂ observed during a LBNP protocol used as a human analog model of hemorrhage. Perhaps of more significance was the accuracy of the model in predicting the blood volume reductions classified by Cooke et al. at varying stages of LBNP (Table 1).¹⁷ Based upon this validation, the model might be considered to reliably serve as a computational platform for analyzing physiologic mechanisms and exploring clinical concepts surrounding the diagnosis and treatment of the compensatory phase of pre-shock prior to the development of frank hemorrhagic shock.

When a physiologic system under study is complex, nonlinear or involves homeostatic feedback mechanisms, it is imperative that the description and analysis must also reflect a high degree of sophistication.^{1,2,4–6} Simple verbal descriptions of homeostatic biological systems can be inadequate because of the difference between the sequential nature of language and the simultaneous character of biologic processes. Even detailed visual models are unable to capture the dynamic quality of physiologic systems analysis. Mathematical models can operate as a formal statement of hypothesis concerning proposed mechanisms of physiological functioning and can demonstrate interactions among biologic variables that may not be intuitively obvious otherwise. Using complex computer-based models in a systems analysis approach, scientists have been able to postulate unforeseen mechanisms for common diseases states such as hypertension and Type II diabetes mellitus before they were demonstrated experimentally.^{7,8,34} However, these computational models must accurately reproduce experimental results before they can be considered as a reliable platform for advanced analysis. If we consider validation as the confirmation that the computer model is accurate within its domain of applicability and intended use, then the computational platform used in this study should be appropriate for the study of hemorrhage. But validation is not the only criterion required to secure confidence that a model may be used in hypothesis formulation and to delineate the underlying mechanisms responsible for the observed experimental findings. The significance of the outputs of a computer model of physiologic functioning is dependent upon the degree of complexity and detail used in its construction.^{4,5} The model used in the current study is unique in that it is founded upon basic physical principles and well-established physiologic relationships rather than simple curve fitting techniques. This higher degree of complexity in model structure provides for a greater assurance in the integrity of simulation results and the ability of the platform to delineate physiologic mechanisms.

5. Limitations

There are several noted limitations. Though the computational platform was able to accurately predict the dynamic changes in CO within the 5% range of MDPE, it fell outside of the SEM at 4 points in the course of changing LBNP. There are several possible reasons for the discrepancies seen. CO is noted to be very capricious as a physiologic parameter with a variability of 9.7% when measured continuously over a 30 min period.³⁵ Impedance

cardiography as a measurement technique for CO may also have some limitations in the range of very low cardiac outputs.²⁰ This is also the range where there is the greatest discordance between the model predicted and experimental results.

Since validation is defined in the context of intended use, it is difficult to develop a universal prescription for determining the level of accuracy required. This level may also differ between research and clinical considerations. The value of 5% discrepancy was chosen because it coincides with a 95% confidence range; however, a greater or lesser degree of accuracy might be necessary.

Just because a model is found to accurately predict global parameters does not validate the model for all other parameters or the mechanisms of model functioning. There may also be limitations in the accuracy of the model outside of the range that was used in these validation comparisons. It is important that the model undergo continuing scrutiny particularly if it ever fails to match experimental reality.

This study presents a first-step validation assessment of a computational platform for the analysis of physiologic state during hemorrhage, a common clinical pathology. The computer model was found to accurately predict the experimental results observed using an LBNP protocol as an analog of hemorrhage. The model should be further validated and explored as a platform for studying concepts and physiologic mechanisms of hemorrhage including its diagnosis and treatment. Results from such studies may be useful not only in understanding the physiology of hemorrhage but also other states of critical illness.

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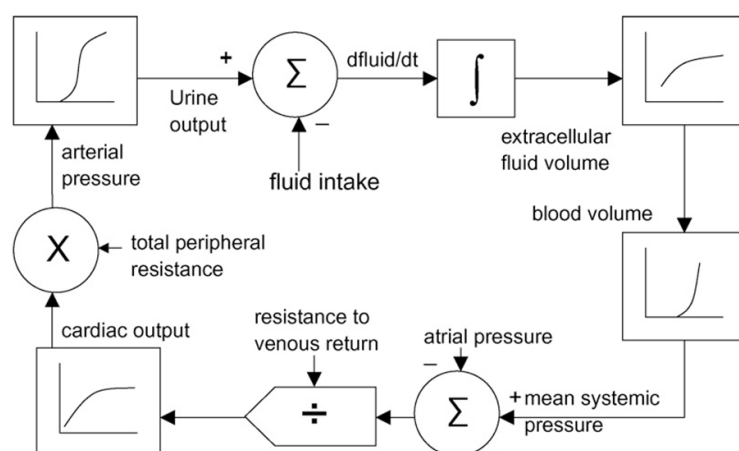


Fig. 1.

This schematic depicts the interrelationships involved in the circulatory control mechanisms within the mathematical model. Within this scheme, the differential of fluid intake and urine output results in an overall change in extracellular fluid volume, blood volume and mean systemic pressure according to known physiologic relationships. The mean systemic pressure drives venous return and the cardiac output through the Starling relationship. The developed systemic arterial pressure and renal arterial perfusion pressure controls urine output and completes the feedback loop. These mechanisms for circulatory control are central to the determination of the parameters validated in the computer simulation study and systems analysis.

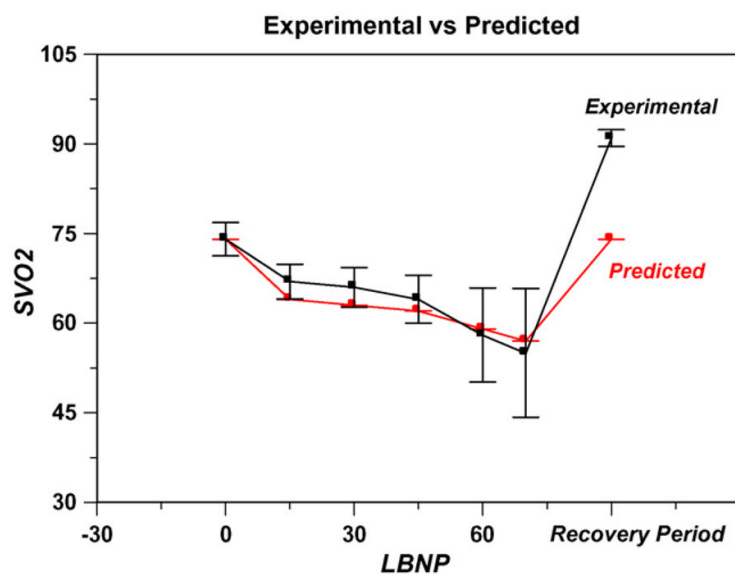


Fig. 2. Dynamic comparison of the values for SVO₂ (central venous oxygen saturation) predicted by the computational platform to those obtained during the course of the experimental LBNP (Lower Body Negative Pressure) protocol.

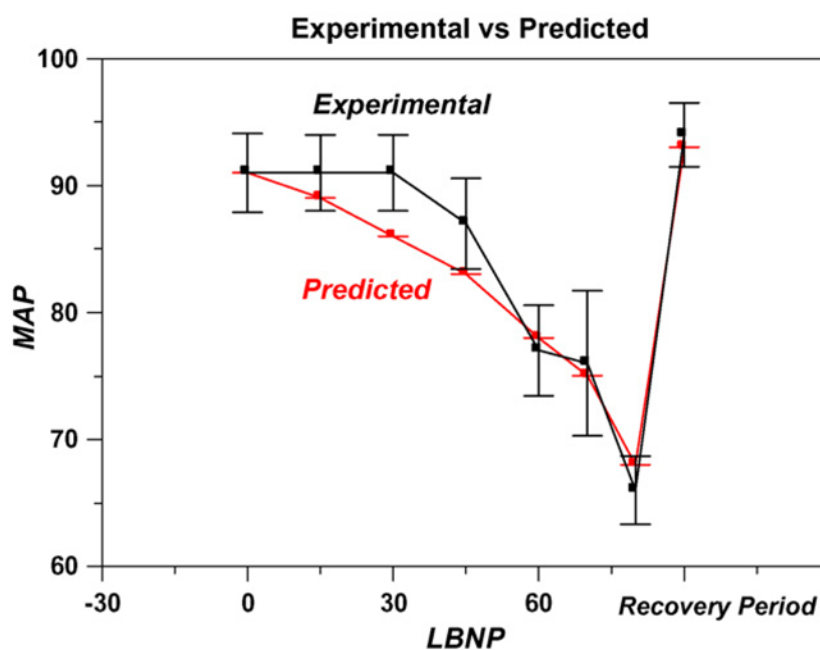


Fig. 3. Dynamic comparison of the values for MAP (mean arterial pressure) predicted by the computational platform to those obtained during the course of the experimental LBNP (Lower Body Negative Pressure) protocol.

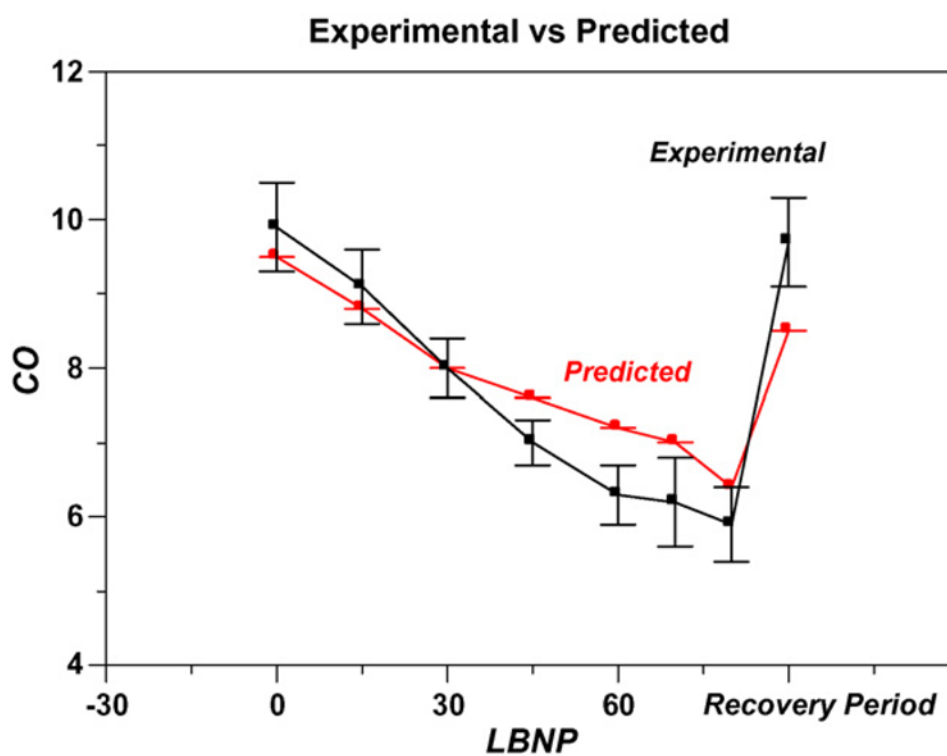


Fig. 4. Dynamic comparison of the values for CO (cardiac output) predicted by the computational platform to those obtained during the course of the experimental LBNP (Lower Body Negative Pressure) protocol.

Table 1

Comparisons of the amount of fluid (blood and plasma) displaced by various pressures in the LBNP methodology to that predicted by the model with similar pressures (in parentheses) and the corresponding standard classification of hemorrhage these displacements represent.

Classification of hemorrhage	Corresponding mmHg LBNP	Amount of fluid displacement	Amount predicted by model
Mild (10% blood loss)	10–20 mmHg	400–550 ml	486 ml (–15 mmHg)
Moderate (10–20% blood loss)	20–40 mmHg	500–1000 ml	664 ml (–30 mmHg)
Severe (>20% blood loss)	>40 mmHg	>1000 ml	938 ml (–60 mmHg)